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<b>(21) International Application Number:</b> PCT/DK94/00145 <b>(22) International Filing Date:</b> 7 April 1994 (07.04.94) <b>(30) Priority Data:</b> 0420/93                      7 April 1993 (07.04.93)                      DK <b>(71) Applicant (for all designated States except US):</b> BUKH MEDITEC A/S [DK/DK]; Lejrvej 39-41, Kirke Værløse, DK-3500 Værløse (DK). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> BAR-SHALOM, Daniel [IL/DK]; Rypevænget 213, DK-2980 Kokkedal (DK). <b>(74) Agent:</b> PLOUGMANN & VINGTOFT A/S; Sankt Annæ Plads 11, P.O. Box 3007, DK-1201 Copenhagen K (DK).		<b>(81) Designated States:</b> AU, BB, BG, BR, BY, CA, CN, CZ, CZ (Utility model), DE (Utility model), DK (Utility model), FI, FI (Utility model), GE, HU, JP, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, SK (Utility model), TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> DRUG ADMINISTRATION SYSTEM		
<b>(57) Abstract</b> <p>A method for parenteral administration of a drug substance comprising penetration of the skin or the mucosa of a human or an animal by a body of an appropriately formed solid pharmaceutical composition is disclosed. The body of the pharmaceutical composition may be needle-shaped so that it is possible to avoid any external penetration equipment when the composition is administered. The composition is preferably made by materials which are biodegradable such as, e.g., materials selected from the group consisting of inorganic salts such as, e.g., calcium, magnesium, bismuth and zinc salts; lipids; carbohydrates, such as, e.g., polysaccharides, sucrose, glucose, agarose, dextrin, cyclodextrin and mixtures thereof; proteins such as, e.g., gelatins, collagens, modified collagens, albumins, caseins and derivatives thereof, and mixtures thereof; natural polymers, synthetic polymers such as, e.g., poly-epsilon-aminocaproic acid, poly-isobutyric acid and derivatives thereof, polylactic acid and derivatives thereof, polyglycolic acid and derivatives thereof, poly(lactide-glycolide)-copolymers and derivatives thereof, polyesters, polyethylene glycols, polypropylene glycols, Pluronic®; and mixtures thereof. Especially gelatin has proved suitable as basic material. A drug delivery system comprising a body of a pharmaceutical composition and supporting means for facilitating the administration is also disclosed.</p>		

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## DRUG ADMINISTRATION SYSTEM

## FIELD OF THE INVENTION

The present invention relates to a method for parenteral administration of a drug substance comprising penetration of the skin or the mucosa of a human or an animal by a body of an appropriately formed solid pharmaceutical composition. The present invention also relates to a body of a solid pharmaceutical composition which has a shape and/or strength which enables it to penetrate unbroken skin or mucosa of a human or an animal in order to deliver an active substance to the animal and to a process for the preparation of this composition. Furthermore, the present invention relates to a novel drug delivery system comprising a solid body of a pharmaceutical composition and to a process for the preparation of such a drug delivery system.

## BACKGROUND OF THE INVENTION

Many different methods and systems for delivery of drug substances are available today.

In general, the oral route is the preferred administration route in that numerous drug substances are readily absorbed from the gastrointestinal tract. This form of administration is easy and well accepted by the patient, and generally results in good patient compliance. However, even though advanced techniques within the field of drug formulation, such as time controlled-release systems, have made it possible to administer a wide range of different types of pharmaceuticals in an acceptable manner, the bioavailability of the drug substance, i.e. the rate of drug absorption and the extent to which the drug substance is absorbed, still depends to a considerable extent on the nature of the active drug substance itself, i.e. on its physical and chemical properties. Accordingly, many drug substances, e.g. numerous pepti-

des, still cannot be administered satisfactorily by the oral route.

An administration route which circumvents the gastrointestinal tract is normally referred to as a parenteral administration route. Parenteral administration is the route of choice for drugs which are degraded or are erratically or unreliably absorbed when administered orally. The parenteral route provides a reliable dose-response relationship. Parenteral administration routes can be divided up into invasive and non-invasive routes, i.e. routes in which delivery of the active drug substance takes place with or without physical disruption of the skin or mucosa, respectively. Examples of non-invasive routes are transcutaneous delivery of a drug substance applied in form of plasters (and in rare cases ointments), and transmucosal delivery, such as nasal administration or sublingual administration whereby the drug substance is protected from first-pass metabolism by the liver. Both the invasive and the non-invasive parenteral administration routes are associated with several disadvantages. For instance, the use of the non-invasive parenteral route is limited to the relatively small number of drug substances which are able to penetrate the skin or mucosa at a sufficient rate. Some of the risks associated with invasive administration are discussed in greater detail below.

The administration of drugs which are intended to reach the vascular or circulatory system of a human or of an animal within a rather short time normally involves an invasive administration route wherein the intact external barrier of the body (the skin or the mucosa) is disrupted or penetrated. Such methods all have specific advantages and disadvantages.

With respect to the invasive route of parenteral administration, it is difficult to make a clear distinction between injections and implants. Nevertheless, it is normally accepted that injection relates to the administration of liquid formulations to the body by means of needles or cathe-

ters, whereas implants are generally employed for administration of formulations in solid form which can be incorporated into the body by various mechanical methods involving the use of some kind of invasive equipment or which can be inserted  
5 into a lesion, e.g. in connection with surgery. In addition, implants are normally employed when sustained release of a drug is desired. Due to the need for rather specialized equipment and skill of the person performing the implantation, this administration route is normally restricted to  
10 situations wherein a special sustained administration is desired or to administration to locations where the blood supply for some reason is limited.

In the patents and literature cited below solid preparations and methods for parenteral administration of such solid  
15 preparations are disclosed.

European Patent No. 139 286 B1 discloses an injectable sustained-release preparation which comprises an active ingredient and a pharmaceutically acceptable proteinaceous biodegradable carrier. The preparation is described as having a  
20 needle-like or bar-like shape. The preparation is employed as an implant which is inserted into the body e.g. by injection, for example by inserting a fine tube (such as a catheter) into the body, and inserting the needle-like shaped preparation via the fine tube, or by inserting the preparation  
25 directly into the body by means of forceps needles which are capable of penetrating the skin. A specific embodiment of a device for administering the preparation is also disclosed which comprises a fine tube and an inner needle. The inner needle is stabbed into a portion of the body, whereafter the  
30 fine tube is inserted into the body by sliding its inner wall along the outer wall of the inner needle. The needle-like preparation is inserted into the body by passing it through the fine tube. Usually the insertion of the preparation into the fine tube is carried out by withdrawing the inner needle  
35 and then pushing the preparation into the body via the fine tube with a pushing pole.

A solid needle-like or bar-like sustained-release preparation suitable for injection is disclosed in US Patents Nos. 5,021,241 and 4,774,091. The preparations comprise a physiologically active ingredient that is unstable to heat and a pharmaceutically acceptable biodegradable protein carrier. The needle-like or bar-like preparations according to the examples disclosed in these patents are formed by compression of the preparation obtained by mixing the active ingredient and the carrier under aqueous condition. It is mentioned that the preparation can be inserted into a body by operation or with a forceps needle for a fibrescope, or via an indwelling needle.

US Patent Nos. 5,081,156 and 4,855,134 disclose sustained-release preparations comprising interferon or indomethacin or a salt thereof as an active ingredient and collagen or gelatin or albumin as a biodegradable carrier, the preparation being in form of powder particles suspended in a viscous solvent suitable for injection, or being in the form of a shaped preparation suitable for use as an injection in a solid state or for implanting into a body. The preparations according to the cited patents are prepared by a process which comprises mixing the active ingredient with the carrier to form a liquid mixture, and drying the resultant mixture. A needle-like or bar-like preparation is formed under compression, and it is mentioned that such preparations can be inserted into a body by operation or with a forceps needle for a fibrescope or via an indwelling needle. It is also mentioned that the preparation may be formed into other conventional sustained-release oral preparations, a medicine for external application, suppositories or the like by conventional techniques.

US Patent No. 4,849,141 discloses a method for preparing a sustained-release formulation. It is mentioned that the formulation may have a variety of sizes and shapes, such as a spherical, hemispherical, column, tubular, or sheet-like shape as well as needle- or bar-like shape. In addition, it

is mentioned in this patent that the formulation may be administered to a living body, for example, by subcutaneous insertion or implantation into a body cavity, depending on the lesional region to be treated. The method for preparing the formulation comprises blending of a physiologically active ingredient together with collagen and/or gelatin using a solvent such as pure water or water in admixture with a hydrophilic organic solvent. It is also mentioned that the formation of fibres in the composition should be avoided.

10 Lin et al. (Biomat., Art. Cells, Art. Org., (1988), 16(4), 801-814 and Biomat., Art. Cells, Art. Org., (1989), 17(2), 189-203) describe controlled release polymeric needle devices containing adriamycin HCl for local treatment of solid tumours. The polymeric needles are made of polylactic acid or  
15 ethylene-vinyl acetate and hydroxypropylmethylcellulose is said to be used as a release regulator.

It appears from the patents and literature cited above that all the solid formulations disclosed therein for parenteral administration should be administered using some sort of  
20 penetrating equipment or means which is separate from and does not form a part of the preparation or formulation itself.

In general, formulations adapted for invasive parenteral administration are administered through catheters or needles  
25 which are used to provide a passageway for the drug substance. The drug substance is normally forced through the needle or catheter by use of a syringe, stiletto, or pushing pole, or simply by gravity.

Among the disadvantages of conventional invasive parenteral administration routes, such as injection through a needle or  
30 via other penetration means, are the direct local pain caused at the site of penetration and the psychological unpleasantness which is generally associated with needles and injections; the latter disadvantages reduce the applicability of

such conventional routes in self-administration. In addition, the necessity for using correct techniques in handling the injection means and carrying out the injection requires special skills on the part of the person performing the administration, especially in the case of intravenous and intramuscular injections.

It is well-known that failure to follow aseptic procedures is a common problem even among trained hospital employees when preparing and administering parenteral medicaments; accordingly, parenteral administration is associated with an appreciable risk of life-threatening septicemia. It is clear that every penetration of the skin or the mucosal barrier is associated with a considerable risk of infection, and accordingly every effort should be made to minimize the necessary number of insertions or penetrations.

Other serious disadvantages in addition to infection are complications due to the unintended introduction of particulate matter, air embolism, and breakage of catheters, needles, or other penetration means used. For example, there is the possibility of injection into the patient of glass particles formed during opening or breakage of ampoules, or of rubber particles cut off by the needle when penetrating the closure (e.g. a septum). Furthermore, there is a risk of infection from contaminated equipment such as used needles.

## SUMMARY OF THE INVENTION

A body of a solid pharmaceutical composition with a shape and consistency enabling it to penetrate the skin would solve most of the above-discussed problems related to invasive parenteral administration. If such a body of a solid pharmaceutical composition consists essentially of the active drug substance itself, its size can be reduced, thus minimizing pain and leaving no superfluous equipment and therefore no risk of infection to others, and, if properly designed, it would be easy to use by the end user. Such a body could be



designed for immediate release or for delayed release of the drug.

The object of the present invention is the provision of such bodies and drug delivery systems.

- 5 In one aspect, the present invention relates to a body of a solid pharmaceutical composition comprising at least one drug substance and having a shape and/or a strength which enables it to penetrate unbroken skin or mucosa of a human or animal in order to deliver said drug substance to an underlying  
10 tissue or into the blood stream of said human or animal.

In another aspect, the invention relates to a method for parenteral administration of a drug substance to a human or an animal, the method comprising:

- i) contacting the skin or the mucosa of said human or animal  
15 with a body of a solid pharmaceutical composition which comprises the drug substance and which has a shape and/or a strength which enables it to penetrate unbroken skin or mucosa in order to deliver said drug substance to an underlying tissue or into the blood stream of the human  
20 or of the animal; and
- ii) penetrating said skin or mucosa with said body so as to position at least a part of said body in said underlying tissue or in said blood stream.

The present invention further relates to a drug delivery  
25 system comprising

- i) at least one body of a solid pharmaceutical composition comprising at least one drug substance and having a shape and/or a strength enabling penetration of unbroken skin or mucosa by said body in order to deliver said drug  
30 substance to an underlying tissue or into the blood stream of a human or of an animal, and
- ii) supporting means adapted to facilitate said penetration.

A further aspect of the present invention relates to a process for the preparation of a body of a pharmaceutical composition comprising:

- 5 i) mixing a material, preferably a polymer material and optionally a filler with an active drug substance,
- ii) extruding the mixture containing the active drug through a die to form an elongated body or, alternatively, shaping the mixture to the body by means of injection moulding,
- 10 iii) drying the body and cutting the body to form a pointed end.

In a still further aspect the invention relates to a process for the preparation of a drug delivery device comprising embedding at least one body of a solid pharmaceutical composition which comprises at least one drug substance and having  
15 a shape and/or a strength which enables it to penetrate unbroken skin or mucosa of a human or animal in a supporting means which is adapted to facilitate said penetration.

#### DETAILED DESCRIPTION OF THE INVENTION

- 20 As appears from the above, a pharmaceutical composition according to the invention should be shaped so as to ensure that penetration of the skin or mucosa results in as little tissue damage (and pain) as possible, while also ensuring that administration is safe and reproducible.
- 25 As mentioned above, the body of a pharmaceutical composition according to the present invention normally has an elongated shape with at least one pointed end. Other shapes may also be used, for example a tetrahedral shape, in which the pointed end will always be opposite a plane surface, thereby facilitating correct administration. Such tetrahedral shaped compositions can easily be administered by pressing the pointed  
30 end of the composition against the skin or mucosal surface to be penetrated, pressure being applied to the opposite plane surface e.g. using the tip of a finger.

Quite generally, the body of a pharmaceutical composition according to the invention can have any shape which, taking into consideration the strength of the body in question, enables the body to penetrate the mucosa or skin in order to deliver an active drug substance to the underlying tissue or a blood vessel. Though an elongated or otherwise pointed shape normally will be most suitable, the size of the body also influences its penetration properties. Accordingly, it is contemplated that bodies having other shapes, e.g. spherical, may be able to penetrate the mucosa or skin when the bodies are very small.

The cross sectional shape of the elongated bodies will often be circular, but other cross sectional shapes will also be suitable, such as an oval, a triangle, a quadrangle a pentagon, etc. An elongated body whose cross section has defined edges, e.g. a triangle or square, will also facilitate easy penetration of the skin or mucosa. In some case an elongated form with a hook shaped penetrating end may be preferred so that the body cannot be retrieved after penetration.

In a preferred embodiment of the invention, the body of the solid pharmaceutical composition has the needle-shaped described above, which allows easy penetration of the skin without any use of some kind of penetrating equipment apart from the composition itself.

Other possibilities are for example a thicker "nail-like" shape or needles mounted in a strip adapted to facilitate administration with automatic equipment. Such bodies would be suited to be applied with the help of an instrument for serial administration (i.e. for vaccination, veterinary uses, etc.).

Three different areas for administration are contemplated: The skin, the mucosa (especially the oral mucosa), and the blood vessels.

The skin is clearly easily accessible, and because of its large surface area, areas where pain or discomfort is minimal can be identified. Also, finding new sites where no drug has previously or recently been administered is easy. The skin  
5 normally repairs itself easily as evidenced by the relative rapid healing following injections.

Blood vessels represent a particular case of administration through the skin in which the target is a vein or artery. Special steps must be taken to ensure access to the blood  
10 vessels (see the description below and Fig. 4). Other target organs and sites for administration according to the invention are intrapenile, intralesional (tumours, papules, psoriatic plaques, acne cysts, warts, intradermal parasites, vesicles, scar tissue, keloids, cellulitis, furuncles, nails,  
15 bullae, hyper- or hypopigmented areas, angiomas, etc.) or into any organ accessible through the skin (testicles, corpus cavernosum, thyroid glands, etc.). Also administration to body cavities such as intra-articular, intraperitoneal, etc. will in some situations be of interest.

20 Mucosa have a very rich blood supply, and the oral mucosa is a particularly suitable administration site according to the invention, especially when it is desirable that the active drug substance enters the oral venous drainage system to the right heart and bypasses the stomach and liver, thus avoiding  
25 first-pass destruction of the drug. For purposes of the present invention it is desirable that the capillaries are very close to the surface, such as in the mucosa, whereby the length of penetration of the body of a solid composition according to the invention need not be longer than about  
30 2 mm. For administration to the skin, the alveolar connective tissue below the skin has to be reached, and accordingly, the body of the solid composition according to the invention should preferably be about 3 mm long.

Preferred routes of administration according to the invention  
35 are subcutaneous injection (i.e. under the skin), submucosal

injection (i.e. under the mucosa), intradermal injection (i.e. within the vascular inner layer of the skin, this route usually being employed for a local action within the skin such as in skin tests), intramucosal injection (i.e. within  
5 the mucosa), intramuscular injection (i.e. within a muscle), intravenous injection (i.e. within a vein), and intra-arterial injection (i.e. within a artery).

In an interesting embodiment of the invention the body contains the active substance or drug alone, which allows a  
10 larger amount of the active ingredient to be administered using a given size body. The active substance will generally not be able to be moulded into a needle strong enough and with the right volume to penetrate the skin or mucosa alone. Therefore, the most common implementation comprises of a  
15 material to give strength (such as, e.g., a polymer material), optionally together with a filler to compensate for different dosages in addition to the drug. This enables the formulation of a needle to easily be adapted to new drugs. One such preferred polymer is gelatin, since it is regarded  
20 as being innocuous and because it fulfils the requirements of strength and solubility in body fluids. The filler is e.g. a sugar which also imparts improved physical properties to the gelatin.

The invention is particularly suitable for the administration  
25 of active substances which are digested in the gastrointestinal tract or which are labile in an aqueous medium or an aqueous environment. In a composition according to the invention, the active substance is embedded or encapsulated in a body which is substantially dry and in such a medium  
30 degradation of the active substance with respect to e.g. hydrolysis cannot take place.

The expression "active substance" as used herein broadly includes any compound, or mixture thereof, that can be delivered from the composition to produce a beneficial result.  
35 The active and beneficial agents include pharmaceutically or

physiologically active substances (drugs), food supplements, nutrients, cosmetics, vitamins, and other agents that benefit the environment in which they are used.

In the present context, the term "drug" and "drug substance" include any physiologically or pharmacologically active substance that produces a localized or systemic effect in animals, in particular mammals, including humans and primates. Other animals include domestic household, sport or farm animals such as sheep, goats, cattle, horses and pigs, laboratory animals such as mice, rats and guinea pigs, fishes, to avians, reptiles and zoo animals.

A number of active drug substances which may be delivered according to the invention are listed below:

Hormones and their derivatives such as:

- 15 - hypothalamus hormones
- pituitary gland hormones such as growth hormone, oxytocin, and LH-RH
- adrenal hormones, corticosteroids and derivatives thereof
- 20 - thyroid gland hormones such as calcitonin
- gastrointestinal hormones and derivatives thereof
- pancreatic hormones and derivatives thereof such as insulin and glucagon
- cardiovascular regulatory hormones such as natriuretic hormone
- 25 - sex hormones

Proteins including adhesive matrix proteins such as, e.g., fibronectin, vitronectin, laminin, collagens, thrombospondin; growth factors such as, e.g., acidic and basic fibroblast growth factor (acidic FGF and basic FGF, respectively), interleukin-2 (int-2), hst/ks, FGF-5, FGF-6, keratinocyte growth factor (KGF), heparin-binding epidermal growth factor (HB-EGF), vascular endothelial growth factor (VEGF), tumour growth factors (TGF), plate-

- let derived growth factor (PDGF) and interferon  $\gamma$ ; proteins involved in lipid metabolism such as, e.g., lipoprotein lipase, hepatic triglyceride lipase, apolipoprotein B, apolipoprotein E; serine protease inhibitors such as, e.g., antithrombin III, heparin co-factor II, protease nexins; and other proteins such as, e.g., superoxide dismutase, elastase, platelet factor 4, N-CAM, viral coat protein, transcription fractions, coagulase enzymes;
- 10 CNS-stimulants, anxiolytics, sympatomimetics, parasympatomimetics, parasympatolytics, vasoconstrictors and vasodilators, antineoplastic, antiviral drugs and antitumour drugs, anoretics, antimimitics, anasthetics, analgetica, antibiotics, anti-allergic drugs, anticholinergics, anti-
- 15 depressants, antiepileptica, antiinflammatory drugs, vasoactive drugs, cardial active drugs, blood factors, antihypertensiva, prostaglandins, growth factors, cytokines such as interferons, enzymes, including enzymes associated with lysomal defects, vaccines, including
- 20 antibodies, diagnostic drugs such as substances used for skin tests, vitamins such as vitamin D, and nutrients.

Examples of specific active substances are:

- Codeine, ethylmorphine, dextromethorphan, noscapine, pentoxiverine, acetylcysteine, bromhexine, epinephrine, isoprenaline,
- 25 ne, orciprenaline, ephedrine, fenoterol, rimiterol, ipratropium, cholinetheophyllinate, proxiphylline, beclomethasone, budesonide, deslanoside, digoxine, digitoxin, disopyramide, proscillaridin, chinidine, procainamide, mexiletin, flecainide, alprenolol, propranolol, nadolol, pindolol, oxprenolol,
- 30 labetalol, timolol, atenolol, pentaeritryltetranitrate, isosorbiddinitrate, isosorbidmononitrate, niphedipin, phenylamine, verapamil, diltiazem, cyclandelar, nicotinylalcohol, inositolnicotinate, alprostadil, etilephrine, prenalterol, dobutamine, dopamine, dihydroergotamine, guanetidine, betanidine,
- 35 dine, methyldopa, reserpine, guanfacine, trimethaphan, hydra-

lazine, dihydralazine, prazosine, diazoxid, captopril, nifedipine, enalapril, nitroprusside, bendroflumethiazide, hydrochlorthiazide, metychlothiazide, polythiazide, chlorthalidon, cinetazon, clopamide, mefruside, metholazone, bumetanide, 5 ethacrynacide, spironolactone, amiloride, chlofibrate, nicotinic acid, nicheritrol, brompheniramine, cinnarizine, dexchlorpheniramine, clemastine, antazoline, cyproheptadine, promethazine, cimetidine, ranitidine, sucralfat, papaverine, moxaverine, atropine, butylscopolamin, emepron, glucopyrron, 10 hyoscyamine, mepensolar, methylscopolamine, oxiphencyclimine, probanteline, terodilin, sennaglycosides, sagraadaextract, dantron, bisachodyl, sodiumpicosulfat, etulos, diphenolxylate, loperamide, salazosulfapyridine, pyrvin, mebendazol, dimeticon, ferrofumarate, ferrosuccinate, ferritetrasemi- 15 sodium, cyanochochobalamine, folic acid heparin, heparin cofactor, diculmarole, warfarin, streptokinase, urokinase, factor VIII, factor IX, vitamin K, thiotepa, busulfan, chlorambucil, cyclophosphamid, melfalan, carmustin, mercaptopurin, thioguanin, azathioprin, cytarabin, vinblastin, vin- 20 christin, vindesin, procarbazine, dacarbazine, lomustin, estramustin, teniposide, etoposide, cisplatin, amsachrin, aminogluthetimid, phosphestrol, medroxiprogresterone, hydroxiprogresterone, megesterol, noretisteron, tamoxiphen, ciclosporin, sulfisomidine, bensylpenicillin, phenoxymethylpenicillin, 25 dicloxacillin, cloxacillin, flucloxacillin, ampicillin, amoxicillin, pivampicillin, bacampicillin, piperacillin, mezlocillin, mecillinam, pivmecillinam, cephalotin, cephalexin, cephradine, cephadroxil, cephaclor, cefuroxim, cefotaxim, ceftazidim, cefoxitin, aztreonam, imipenem, cilastatin, 30 tetracycline, lymecycline, demeclocycline, metacycline, oxitetracycline, doxycycline, chloramphenicol, spiramycin, fusidic acid, lincomycin, clindamycin, spectinomycin, rifampicin, amphotericin B, griseofulvin, nystatin, vancomycin, metronidazole, tinidazole, trimethoprim, norfloxacin, salazosulfapyridine, 35 aminosalicylic acid, isoniazid, etambutol, nitrofurantoin, nalidixic acid, metenamine, chloroquin, hydroxichloroquin, tinidazol, ketokonazol, acyclovir, interferon idoxuridin, retinol, tiamin, dexpantenol, pyridoxin, folic acid, ascorbic



acid, tokoferol, phytominadion, phenfluramin, corticotropin, tetracosactid, tyrotropin, somatotropin, somatrem, vasopressin, lypressin, desmopressin, oxytocin, chloriongonadotropin, cortison, hydrocortison, fludrocortison, prednison, prednisolon, fluoximesteron, mesterolone, nandrolon, stanozolol, oximetolon, cyproteron, levotyroxin, liotyronin, propylthiouracil, carbimazol, tiamazol, dihydrotachysterol, alfacalcidol, calcitriol, insulin, tolbutamid, chlorpropamid, tolazamid, glipizid, glibenclamid, phenobarbital, methyprylon, pyrityldion, meprobamet, chlordiazepoxid, diazepam, nitrazepam, oxazepam, dikaliumchlorazepat, lorazepam, flunitrazepam, alprazolam, midazolam, hydroxyzin, chlormethiazol, propionmazine, alimemazine, chlorpromazine, levomepromazine, acetophenazine, fluphenazine, perphenazine, prochlorperazine, trifluoperazine, dixyrazine, thioridazine, periciazin, chlorprothixene, zuclopentizol, flupentizol, thithixen, haloperidol, trimipramin, opipramol, chlormipramin, desipramin, lofepramin, amitriptylin, nortriptylin, protriptylin, maprotilin, coffein, cinnarizine, cyclizine, dimenhydrinate, meclozine, prometazine, thiethylperazine, metoclopramide, scopolamine, phenobarbital, phenytoine, ethosuximide, primidone, carbamazepine, chlonazepam, orphenadrine, atropine, bensatropine, biperiden, metixene, procylidine, levodopa, bromocriptin, amantadine, ambenon, pyridostigmine, synstigmine, disulfiram, morphine, codeine, pentazocine, buprenorphine, pethidine, phenoperidine, phentanyl, methadone, piritramide, dextropropoxyphene, ketobemidone, acetylsalicylic acid, phenazone, phenylbutazone, azapropazone, piroxicam, ergotamine, dihydroergotamine, cyproheptadine, pizitifen, flumedroxon, allopurinol, probenecid, sodiummaurothiomalate auronofin, penicillamine, estradiol, estradiolvalerianate, estriol, ethinylestradiol, dihydrogesteron, lynestrenol, medroxiprogesterone, noretisterone, cyclophenile, clomiphene, levonorgestrel, mestranol, ornidazol, tinidazol, ekonazol, chlortrimazol, natamycine, miconazole, sulbentin, methylergotamine, dinoprost, dinoproston, gemeprost, bromocriptine, phenylpropanolamine, sodiumchromoglicate, azetazolamide, dichlophenamide, betacarotene, naloxone, calciumfolinate, in particular

clonidine, theophylline, dipyradamol, hydrochlorthiazide, scopolamine, indomethacine, furosemide, potassium chloride, morphine, ibuprofen, salbutamol, terbutalin.

The drug substance which is incorporated in a pharmaceutical composition according to the invention can be in various forms, such as uncharged molecules, molecular complexes, a pharmacologically acceptable salt such as a hydrochloride, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrite, nitrate, borate, acetate, maleate, tartrate, oleate, and salicylate. For acid drugs, salts of metals, amines, amino acids or organic cations, quaternary ammonium, can be used. Derivatives of drugs such as esters, ethers and amides can be used alone or mixed with other drugs and after their release from the composition they may be converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original form, or to a biologically active form.

One class of active drugs which are particularly suitable for administration according to the invention are interferons such as  $\alpha_I$ -,  $\alpha_{II}$ -,  $\beta$ - and  $\gamma$ -interferons.

The dose of the active drug to be used in each particular case will of course depend upon the effect to be achieved and the intended use.

As appears from the above, a body of a pharmaceutical composition according to the invention or at least a part of it must have a sufficient strength to enable penetration of skin or mucosa. Suitable examples of materials which can form the basis of the body of a pharmaceutical composition according to the invention and/or which may be added to another basic material for such a body and/or which may increase the strength of such a body are inorganic salts such as, e.g., calcium, magnesium, bismuth or zinc salts; lipids; carbohydrates; proteins such as, e.g., gelatins, collagens, modified collagens, albumins, caseins and derivatives thereof; natural polymers; synthetic polymers such as, e.g., poly-epsilon-

aminocaproic acid, poly-isobutyric acid and derivatives thereof, polylactic acid and derivatives thereof, polyglycolic acid and derivatives thereof, poly(lactide-glycolide)-copolymers and derivatives thereof, polyesters, polyethylene glycols, polypropylene glycols, Pluronic®; and mixtures thereof. Suitable carbohydrates include polysaccharides, sucrose, glucose, agarose, dextrin and cyclodextrin.

An interesting embodiment according to the invention is a body comprising the carbohydrate in crystalline or caramelized form.

Other suitable carbohydrates are celluloses, cellulose derivatives, modified celluloses, modified cellulose derivatives and mixtures thereof.

To further improve the strength of the penetrating end or other parts of the body, a higher concentration of a strength-improving material can be incorporated, either as a core in the body or applied as a cap at the penetration end portion or covering the hole body. The strength-improving material can also be distributed uniformly throughout the body or in defined layers or zones within the body.

One way of measuring the strength of the body is to measure the compressive strength of the body, i.e. the pressure per unit area which can be applied to a sample of the body before it breaks. The compressive strength of bodies according to the present invention is usually at least about  $15 \times 10^3$  pounds/sq in. With increasing compressive strength of the materials used, the size of the composition can be decreased. The specific compressive strength of each individual composition will depend on the active drug itself as well as the other components and the manner in which the composition is prepared. The compressive strength is preferably at least about  $30 \times 10^3$  pounds/sq in. For some embodiments according to the invention the compressive strength will be at least about  $50 \times 10^3$  pounds/sq in. or even at least about  $80 \times 10^3$

pounds/sq in. or as much as at least  $100 \times 10^3$  pounds/sq in. For compositions comprising carbohydrates in caramelized form the compressive strength of the compositions is very often more than  $100 \times 10^3$  pounds/sq in.

- 5 Due to the fact that a pharmaceutical composition according to the invention is to penetrate the skin or mucosa, the material for preparation of the pharmaceutical composition is preferably biodegradable or substantially biodegradable and/or soluble or substantially soluble in an aqueous medium.
- 10 The choice of material for preparation of a pharmaceutical composition according to the invention depends primarily on the nature of the active drug substance, i.e. its physical and chemical structure. As a consequence of the variation in the physical and chemical properties of the materials men-
- 15 tioned above, a given material may have different effects in different compositions, and different materials can therefore act e.g. as fillers or carriers.

The compositions according to the invention may further comprise various pharmaceutically acceptable excipients.

- 20 One or more excipients may be added to modify the dissolution rate after administration, for example by increasing the content of water in the area of delivery by osmotic force. Examples of such dissolution rate modifiers are monosaccharides, disaccharides, oligosaccharides, gellans, cyclodextrins,
- 25 and mixtures thereof which can enhance the dissolution of drug substances such as, e.g., insulin.

- To increase the absorption rate from the site of delivery, penetration enhancers can be added to the composition. The penetration enhancer may e.g. be an enzyme, for example a
- 30 catabolic enzyme which acts by cleaving components of the supporting matrix of the tissue, thereby increasing the flow rate of body fluids through the tissue. Examples of such enzymes are proteases, lipases and deoxyribonucleases. Speci-

fic enzymes which may be employed are for example amylase, dextranase, hyaluronidase, brinolase, bromelains, pancreatin, chymopapain, chymotrypsins, papain, pepsin, plasmin, rennet, trypsin, urokinase, dease, streptodornase, streptokinase, 5 pancrealipase, muramidase, and mixtures thereof.

An interesting embodiment of the invention is a pharmaceutical composition from which the drug substance is freely released, in contrast to sustained released compositions. In the context of the present invention the term "free release" 10 refers to situations in which no excipient has been added to the composition for the purpose of influencing the delivery rate of the active substance from the composition itself. In other words, the release profile of the drug is substantially unaltered by the composition containing it. When an excipient 15 that influences the release is added, this is referred to as "modified release". This includes excipients which either increase or decrease the rate of release. Examples of types of modified release are sustained release, where the drug is released over a prolonged period, and pulsed release, where 20 the release is not continuous, but rather occurs in pulses or bursts.

A body of a pharmaceutical composition according to the invention may be prepared by means of extrusion or injection moulding, i.e. the material forming the basis of the body is 25 preferably able to undergo an extrusion process or an injection moulding process.

In another aspect, the invention relates to a drug delivery system or device comprising

- 30 i) at least one body of a solid pharmaceutical composition comprising at least one drug substance and having a shape and/or a strength enabling penetration of unbroken skin or mucosa by said body in order to deliver said drug substance to an underlying tissue

- or into the blood stream of a human or of an animal,  
and  
ii) supporting means adapted to facilitate said penetration.

5 A device constituting the drug delivery system of the present invention will thus comprise a supporting means. In principle all types of supporting means may be employed according to the invention including supporting means where the body of the pharmaceutical composition according to the invention,  
10 preferably in the form of a needle, is driven through a cylindrical device such as a piston-like device. The supporting means may typically of a compressible or contractible material, often a sponge or sponge-like material, in which one or more often needle-shaped bodies containing the drug  
15 are embedded.

Administration of the drug takes place by first placing one side of the device in contact with the skin or mucosa through which the drug is to be administered. The actual administration of the drug is accomplished by applying pressure, e.g.  
20 using a finger or a hand, thereby compressing the supporting material. This in turn leads to penetration of the skin by the needles or other bodies containing the drug and thus to release of the drug in the underlying tissue or blood stream. The pressure applied to administer the drug is typically  
25 applied to the side of the device opposite the skin or mucosa. However, another possibility is to apply pressure indirectly. This possibility can for example be used when the drug is to be administered via the oral mucosa. In this case, the device may be placed in the mouth of the patient in such  
30 a manner that one side of the device (i.e. the side through which the drug is to be delivered) is in contact with the inner side of the cheek, while the opposite side of the device is in contact with the teeth and/or gum. Compression of the supporting material and administration of the drug can  
35 in this case be obtained by applying pressure on the outside of the cheek.

The foam or sponge of the supporting means is optionally covered on the surface which is to be in contact with the skin or mucosa with an adhesive and/or disinfecting material. The opposite surface is preferably covered by a backing  
5 designed to effectively transfer pressure to the needles, e.g. of a rigid, non-flexible material. In one embodiment of a drug delivery system according to the invention, the material in which the needle or other body is embedded comprises components which are substantially biodegradable  
10 and/or which can be swallowed by the patient with no significant discomfort.

In a drug delivery system containing one or more needles or other bodies, the needles or bodies are embedded in a supporting means such as a foam or sponge designed to insulate  
15 them from the environment, in particular from humidity and from contamination. The supporting means may also be in the form of a plate, a pad, a patch, a disc, a strip, or a plaster. The structure of the supporting device should allow displacement of the needle in the needle's axial direction  
20 but not to the sides, thus guiding the needle into the skin and preventing it from breaking due to pressure applied during administration of the drug. The supporting means is preferably made of a compressible or collapsible material and preferably has at least one surface covered by a backing  
25 which preferably cannot be penetrated by the needle or other body containing the drug. The backing may be flexible or non-flexible. The supporting means may contain or may have a surface covered with a disinfecting material. The surface which is to be in contact with the skin or mucosa may further  
30 be covered with an adhesive material to facilitate placement.

In the case of intravenous administration, the side of the supporting means facing the skin or mucosa may have a concave shape to ensure that the blood vessel into which the drug is to be administered remains fixed and does not slip or move in  
35 the subcutaneous tissue, thus allowing the needle containing

the drug to penetrate the thickest part holding the vein or artery (confer Fig. 4).

The supporting means may be made of any suitable material such as, e.g., gums such as guar gum, locust bean gum, gum  
5 arabic, agar, carrageenan, liquorice, open cell polyurethane foam, synthetic and/or natural rubber and their foams, celluloses and derivatives thereof such as, e.g., methylcellulose, plastic materials and the like.

Crystallized and caramelized sugars may also be used for the  
10 backing of the supporting means. Caramelized sugars are obtained heating sugars in the absence of water heated in a concentrated solution.

It is contemplated that a drug delivery system according to the invention may be prepared by injection moulding which  
15 makes it possible to prepare the body of the pharmaceutical composition according to the invention as well as the supporting means by an economical and relatively simple process.

When appropriate, e.g. for oral mucosal use, flavours and/or sweeteners can be added to the body or the device according  
20 to the invention.

In a further aspect, the invention relates to a method for parenteral administration of a drug substance to a human or an animal, the method comprising:

- i) contacting the skin or the mucosa of said human or animal  
25 with a body of a solid pharmaceutical composition which comprises the drug substance and which has a shape and/or a strength which enables it to penetrate unbroken skin or mucosa in order to deliver said drug substance to an underlying tissue or into the blood stream of the human  
30 or of the animal; and



- ii) penetrating said skin or mucosa with said body so as to position at least a part of said body in said underlying tissue or in said blood stream.

Furthermore, the invention relates to a method for preparing  
5 a body of a pharmaceutical composition according to the invention, the method comprises

- i) mixing a polymer and optionally a filler with an active drug substance,
- 10 ii) extruding the mixture containing the active drug through a die to form an elongated body,
- 10 iii) drying the body and cutting the body to form a pointed end.

The invention also relates to a method for preparing a drug delivery system according to the invention, the method com-  
15 prises embedding at least one body of a solid pharmaceutical composition which comprises at least one drug substance and having a shape and/or a strength which enables it to penetrate unbroken skin or mucosa of a human or animal in a supporting means which is adapted to facilitate said penetra-  
20 tion.

As will be understood, details and particulars concerning the above-mentioned aspects of the invention will be the same as or analogous to the details and particulars concerning the aspects discussed above (i.e. the aspects concerning a body  
25 of a pharmaceutical composition and concerning a drug delivery system), and this means that wherever appropriate, the statements above concerning the pharmaceutical composition or the drug delivery system, their preparation, improved properties and uses apply mutatis mutandis to the other aspects of  
30 the invention.

## DESCRIPTION OF THE DRAWING

The invention is further described below with reference to the drawings in which:

Fig. 1A shows a drug delivery system according to the invention wherein a body of a solid pharmaceutical composition according to the invention 1 is embedded in a compressible or collapsible supporting material 2 having a contact surface 4 adapted to be brought into contact with skin or mucosa 5. The supporting material 2 is covered with a backing 3 made of a flexible material which enables transfer of pressure applied to the backing material 3 to the body 1.

Fig. 1B shows the drug delivery system shown in Fig. 1A after pressure has been applied (as indicated by the arrow in the figure) to the flexible backing material 3 so as to compress the supporting material 2, causing the body 1 to be released from the compressed supporting material 2 and to penetrate the surface 5.

Fig. 2A shows an alternative embodiment of a drug delivery system according to the invention and having a compressible or collapsible supporting material 2 as described in connection with Fig. 1A, but in which the backing material 3 is a substantially rigid, i.e. non-flexible, material.

Fig. 2B shows the drug delivery system as shown in Fig. 2A after pressure has been applied (as indicated by the arrows in the figure) to the substantially rigid backing material 3 so as to compress the supporting material 2, causing the body 1 to be released from the compressed supporting material 2 and to penetrate the surface 5.

Fig. 3A shows an alternative embodiment of a drug delivery system according to the invention and having a compressible or collapsible supporting material 2 as described in connection with Fig. 1A, but in which the backing material 3 is a substantially rigid, i.e. non-flexible, material.

tion with Fig. 2A but in which three bodies 1 are embedded in the supporting material.

Fig. 3B shows the drug delivery as shown in Fig. 3A after pressure has been applied (as indicated by the arrows in the figure) to the substantially rigid backing material 3 so as to compress the supporting material 2, causing the bodies 1 to be released from the compressed supporting material 2 and to penetrate the surface 5.

Fig. 4A and 4B illustrate a modification of the embodiment of a drug delivery system according to the invention as shown in Fig. 2A and 2B and its use in administering a body 1 according to the invention to a blood vessel 6 underlying a surface 5 of skin or mucosa. In this modification, the surface 4 of the supporting material 2 which is to be brought into contact with the skin or mucosa has a concave form adapted to be brought into position above, and substantially match the contour of, that part of the skin or mucosa which overlies the blood vessel which has a lumen 5 and a wall 6 positioned just beneath the skin or the mucosa, the body 1 being located substantially at the bottom of the depression resulting from the concavity of the surface 4. The concave form of the surface 4 thus facilitates positioning of the body 1 relative to the blood vessel 6 and 7 so as to ensure correct penetration of the body 1 through the wall 7 of the blood vessel and into the lumen of the blood vessel 6 upon applying pressure to the backing material 3 in the manner shown in Fig. 3B.

Fig. 5 illustrates the results of an in vivo test in Mini-Pigs. The test is a comparison test between a conventional insulin composition Actrapid® and an insulin-containing composition according to the invention. The results shown in Fig. 5 clearly indicate that a composition according to the invention may replace a conventional product like Actrapid®.

Examples of the formulation of a body according to the invention are described in the following.

## EXAMPLE 1

A saturated solution of gelatin in water is mixed with beta-cyclodextrin to form a paste, an active drug is added and the mixture is extruded through a 0.2 mm die. The resulting cylinder is left to dry until a firm and crystallized consistency is achieved. The dried cylinder is cut diagonally to form a pointed cutting edge.

## EXAMPLE 2

10% gelatin and 1% agarose are mixed with an active drug and the mixture is milled to a particle size of less than 100  $\mu\text{m}$ . The milled mixture is extruded through a needle and then dried and cut as explained in Example 1.

## EXAMPLE 3

General method for preparing pharmaceutical compositions according to the invention

Pharmaceutical compositions according to the invention are prepared by dissolving 10% w/w of gelatin and 2% w/w of gellen in water and left to gellify. The resulting gel is then milled to a particle size of less than 50  $\mu\text{m}$ . The resulting "powder" is mixed with insulin (or any other drug substance) and extruded using a hypodermic syringe. The resulting "spaghetti"-like material is suspended and left to dry in the air, optionally in a desiccator. After 6 hours in the open air, the spaghetti-like material has acquired the desired crystalline structure.

## EXAMPLE 4

Pharmaceutical composition containing insulin - animal testing

Pharmaceutical compositions containing insulin were prepared as described in Example 3 herein and with a content of 5% w/w of methylene blue (i.e. 5% w/w of methylene blue was added to the powder described above).

- 5 Five Mini-Pigs were anaesthetized with Sedaperone® Vet and Dormicum i.m. and immobilized. The pharmaceutical compositions were inserted into the lips in different places (upper lip, lower lip, and commissure) in order to determine the best administration technique. All sites were found to be  
10 useful but the lower lip proved easiest to use.

Four Mini-Pigs, fasting since the previous day, were anaesthetized with Sedaperone® Vet and Dormicum i.m. and a blood sample were taken from each. Two of the pigs were dosed with Insulin, Actrapid®, 0.5 IE/kg, subcutaneously in the  
15 neck behind the ear; the other two were dosed with a pharmaceutical composition prepared as described above and containing about 0.7 IE/kg, into the lower lip (the lip was chosen because it was found that it best resembles human skin), the lip was wiped dry. Further samples were taken at 10, 15, 20,  
20 30, 60, 90, 120, 240, 300, and 360 minutes after application. The results are shown in Fig. 5 as the concentration of glucose in blood versus time after application. The results show that administration of a pharmaceutical composition according to the present invention gives rise to a peak value  
25 of almost the same order of magnitude as the conventional composition Actrapid®.

## CLAIMS

1. A body of a solid pharmaceutical composition comprising at least one drug substance and having a shape and/or a strength which enables it to penetrate unbroken skin or mucosa of a  
5 human or animal in order to deliver said drug substance to an underlying tissue or into the blood stream of said human or animal.
2. A body according to claim 1 which has an elongated shape.
3. A body according to claim 2 which has a skin- or mucosa-  
10 penetrating end portion,
4. A body according to claim 3, wherein said penetrating end portion comprises a material which endows said end portion with sufficient strength to penetrate said skin or mucosa.
5. A body according to claim 1 comprising a material which  
15 endows said body with sufficient strength to enable said penetration.
6. A body according to claim 4 or 5, wherein said material is selected from the group consisting of inorganic salts, lipids, carbohydrates, proteins, natural polymers, synthetic  
20 polymers and mixtures thereof.
7. A body according to claim 6, wherein said material is a carbohydrate selected from the group consisting of polysaccharides, sucrose, glucose, agarose, dextrin, cyclodextrin and mixtures thereof.
8. A body according to claim 7, wherein the carbohydrate is  
25 in crystalline or caramelized form.
9. A body according to claim 6 or 7, wherein said material is a carbohydrate selected from the group consisting of cellulo-

ses, cellulose derivatives, modified celluloses, modified cellulose derivatives and mixtures thereof.

10. A body according to claim 6, wherein said material is a protein selected from the group consisting of gelatins,  
5 collagens, modified collagens, albumins, caseins and derivatives thereof, and mixtures thereof.

11. A body according to any one of the preceding claims, wherein the composition is substantially biodegradable or substantially soluble in an aqueous medium.

10 12. A body according to any one of the preceding claims further comprising a pharmaceutically acceptable excipient.

13. A body according to claim 12, wherein said excipient is selected from the group consisting of cyclodextrins, monosaccharides, disaccharides, oligosaccharides, gellans, and  
15 mixtures thereof.

14. A body according to claim 12, wherein said excipient is an enzyme selected from the group consisting of proteases, lipases and deoxyribonucleases.

15. A body according to claim 14, wherein said enzyme is  
20 selected from the group consisting of amylase, dextranase, hyaluronidase, brinolase, bromelains, pancreatin, chymopapain, chymotrypsins, papain, pepsin, plasmin, rennet, trypsin, urokinase, deanase, streptodornase, streptokinase, pancrea-lipase, muramidase and mixtures thereof.

25 16. A body according to any one of the preceding claims, wherein said drug substance is substantially freely released from the composition, the composition having substantially no effect on the release profile of the drug substance in the tissue or blood stream to which the drug substance is admini-  
30 stered.

17. A body according to any one of claims 1-15, wherein the release profile of the drug substance is modified by one or more excipients in the composition.

18. A body according to claim 17, wherein the drug substance  
5 is sustain-released or pulse-released from the composition.

19. A body according to any one of the preceding claims which has a hardness of at least about  $15 \times 10^3$  pound/sq in, such as at least  $30 \times 10^3$  pound/sq in, such as at least  $50 \times 10^3$  pound/sq in, such as at least  $80 \times 10^3$  pound/sq in or at  
10 least  $100 \times 10^3$  pound/sq in.

20. A method for parenteral administration of a drug substance to a human or an animal, the method comprising:

- 15 i) contacting the skin or the mucosa of said human or animal with a body of a solid pharmaceutical composition which comprises the drug substance and which has a shape and/or a strength which enables it to penetrate unbroken skin or mucosa in order to deliver said drug substance to an underlying tissue or into the blood stream of the human or of the animal; and
- 20 ii) penetrating said skin or mucosa with said body so as to position at least a part of said body in said underlying tissue or in said blood stream.

21. A method according to claim 20 wherein the body has an elongated shape.

25 22. A method according to claim 21 wherein the body has a skin- or mucosa penetrating end portion,

23. A method according to claim 22, wherein said penetrating end portion comprises a material which endows said end portion with sufficient strength to penetrate said skin or  
30 mucosa.



24. A method according to claim 20 wherein the body comprises a material which endows said body with sufficient strength to enable said penetration.

25. A method according to claim 23 or 24, wherein said material is selected from the group consisting of inorganic salts, lipids, carbohydrates, proteins, natural polymers, synthetic polymers and mixtures thereof.

26. A method according to claim 25, wherein said material is a carbohydrate selected from the group consisting of polysaccharides, sucrose, glucose, agarose, dextrin, cyclodextrin and mixtures thereof.

27. A method according to claim 25, wherein the carbohydrate is in crystalline or caramelized form.

28. A method according to claim 25 or 26, wherein said material is a carbohydrate selected from the group consisting of celluloses, cellulose derivatives, modified celluloses, modified cellulose derivatives and mixtures thereof.

29. A method according to claim 25, wherein said material is a protein selected from the group consisting of gelatins, collagens, modified collagens, albumins, caseins and derivatives thereof, and mixtures thereof.

30. A method according to any one of claims 20-29, wherein the composition is substantially biodegradable or substantially soluble in an aqueous medium.

31. A method according to any one of claims 20-30 wherein the body further comprises a pharmaceutically acceptable excipient.

32. A method according to claim 31, wherein said excipient is selected from the group consisting of cyclodextrins, monosac-

charides, disaccharides, oligosaccharides, gellans, and mixtures thereof.

33. A method according to claim 31, wherein said excipient is an a catabolic enzyme selected from the group consisting of  
5 proteases, lipases and deoxyribonucleases.

34. A method according to claim 33, wherein said enzyme is selected from the group consisting of amylase, dextranase, hyaluronidase, brinolase, bromelains, pancreatin, chymopapain, chymotrypsins, papain, pepsin, plasmin, rennet, trypsin,  
10 urokinase, deanase, streptodornase, streptokinase, pancrea-lipase, muramidase and mixtures thereof.

35. A method according to any one of claims 20-34, wherein said drug substance is substantially freely released from the composition, the composition having substantially no effect  
15 on the release profile of the drug substance in the tissue or blood stream to which the drug substance is administered.

36. A method according to any one of claims 20-34, wherein the release profile of the drug substance is modified by one or more excipients in the composition.

20 37. A method according to claim 36, wherein the drug substance is sustain-released or pulse-released from the composition.

38. A method according to any one of claims 20-37 wherein the a hardness of said body is between about  $15 \times 10^3$  pound/sq in  
25 and  $100 \times 10^3$  pound/sq in.

39. A drug delivery system comprising

i) at least one body of a solid pharmaceutical composition comprising at least one drug substance and having a shape and/or a strength enabling penetration  
30 of unbroken skin or mucosa by said body in order to deliver said drug substance to an underlying tissue

or into the blood stream of a human or of an animal,  
and

- ii) supporting means adapted to facilitate said penetration.

5

40. A drug delivery system according to claim 39, wherein the supporting means is made of a compressible material.

41. A drug delivery system according to claim 39, wherein the supporting means is made of a collapsible material.

- 10 42. A drug delivery system according to any one of claims 39-41 wherein the supporting means is in form of a plate, a pad, a patch, a disc, a strip, a sponge, a foam or a plaster.

43. A drug delivery system according to any one of claims 39-42 wherein the supporting means has a surface covered by a  
15 backing of a flexible material.

43. A drug delivery system according to any one of claims 39-42 wherein the supporting means has a surface covered by a backing of a substantially non-flexible material.

44. A drug delivery system according to any one of claims 39-  
20 43 wherein the supporting means has a concave surface.

45. A drug delivery system according to any one of claims 39-44 wherein the supporting means has a surface covered with an adhesive material and/or a disinfecting material.

- 25 46. A drug delivery system according to any one of claims 39-45 wherein the supporting means is substantially biodegradable or substantially soluble in an aqueous medium.

47. A body according to any one of claims 1-19 for use in a drug delivery system according to claim 39.

48. A process for the preparation of a body of a pharmaceutical composition comprising:

- i) mixing a polymer and optionally a filler with an active drug substance,
- 5 ii) extruding the mixture containing the active drug through a die to form an elongated body,
- iii) drying the body and cutting the body to form a pointed end.

49. A process for the preparation of a body of a pharmaceutical composition according to claim 48 further comprising  
10 adding at least one pharmaceutically acceptable excipient to the mixture, said excipient being selected from the group consisting of dissolution modifying substances, diffusion modifying substances, penetrating enhancers, or strength-  
15 improving materials and mixtures thereof.

50. A process for the preparation of a drug delivery device comprising embedding at least one body of a solid pharmaceutical composition which comprises at least one drug substance and having a shape and/or a strength which enables it to  
20 penetrate unbroken skin or mucosa of a human or animal in a supporting means which is adapted to facilitate said penetration.

51. A process according to claim 50 wherein the supporting  
25 means is made of a compressible material.

52. A process according to claim 50, wherein the supporting means is made of a collapsible material.

53. A process according to any one of claims 50-52 wherein the supporting means is in form of a plate, a pad, a patch,  
30 a disc, a strip, a sponge, a foam or a plaster.

54. A process according to any one of claims 50-53 wherein the supporting means has a surface covered by a backing of a flexible material.

55. A process according to any one of claims 50-53 wherein the supporting means has a surface covered by a backing of a substantially non-flexible material.

5 56. A process according to any one of claims 50-55 wherein the supporting means has a concave surface.

57. A process according to any one of claims 50-56 wherein the supporting means has a surface covered with a adhesive material and/or a disinfecting material.

10 58. A process according to any one of claims 50-57 wherein the supporting means is substantially biodegradable or substantially soluble in an aqueous medium.

59. Use of a body according to any one of claims 1-19 for the process according to claim 50.

15 60. A body according to any of claims 1-9 and 47 or to the method according to any of claims 20-38, or to the drug delivery system according to any of claims 39-46, or to the process according to any of claim 48-59 wherein the active drug is an interferon such as  $\alpha_I$ -,  $\alpha_{II}$ -,  $\beta$ - or  $\gamma$ -interferon.

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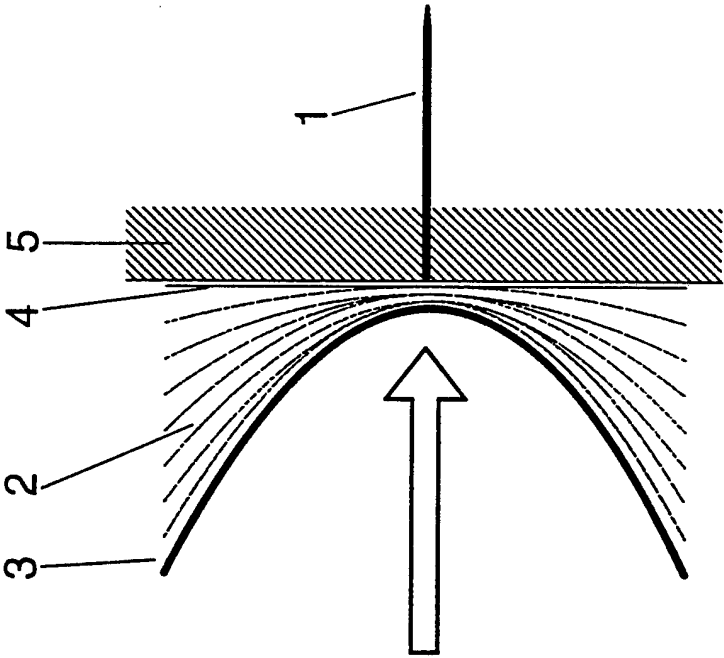


Fig. 1B

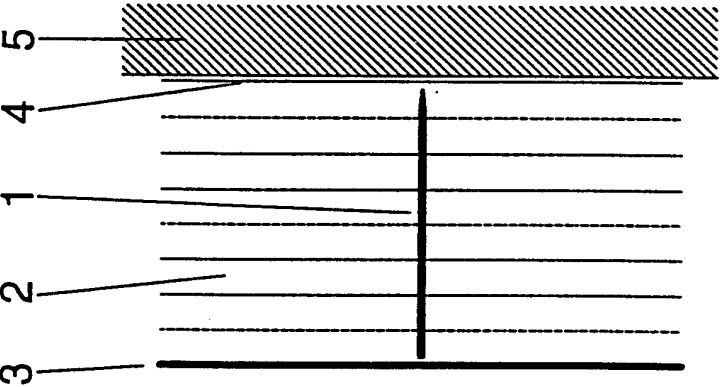


Fig. 1A

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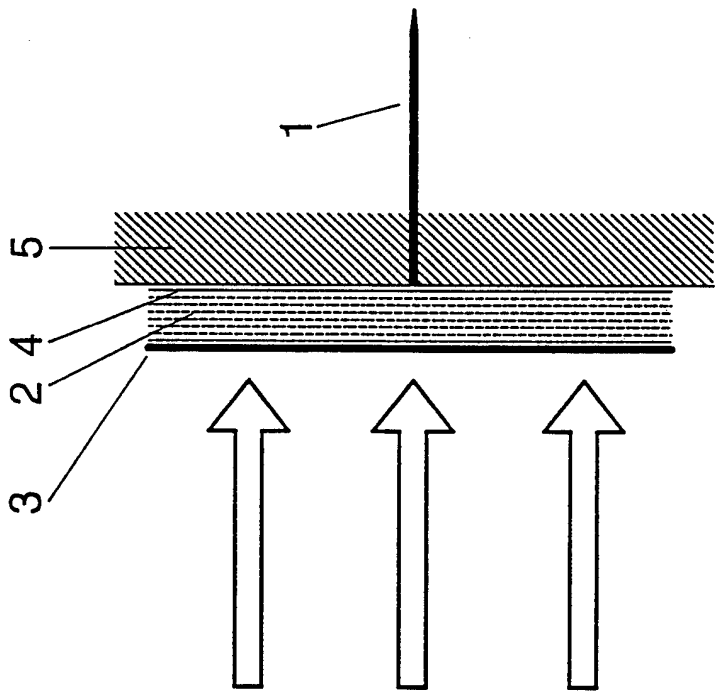


Fig. 2B

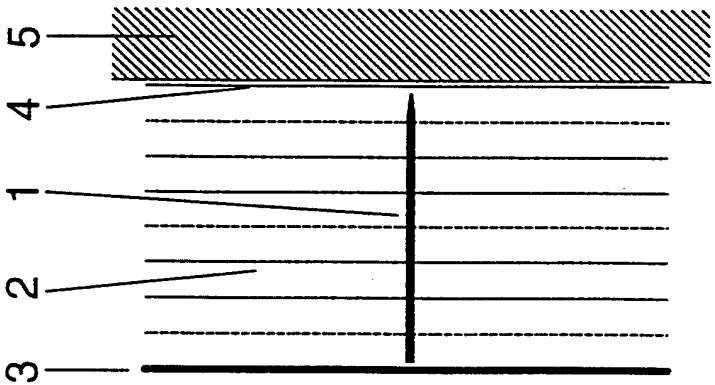


Fig. 2A

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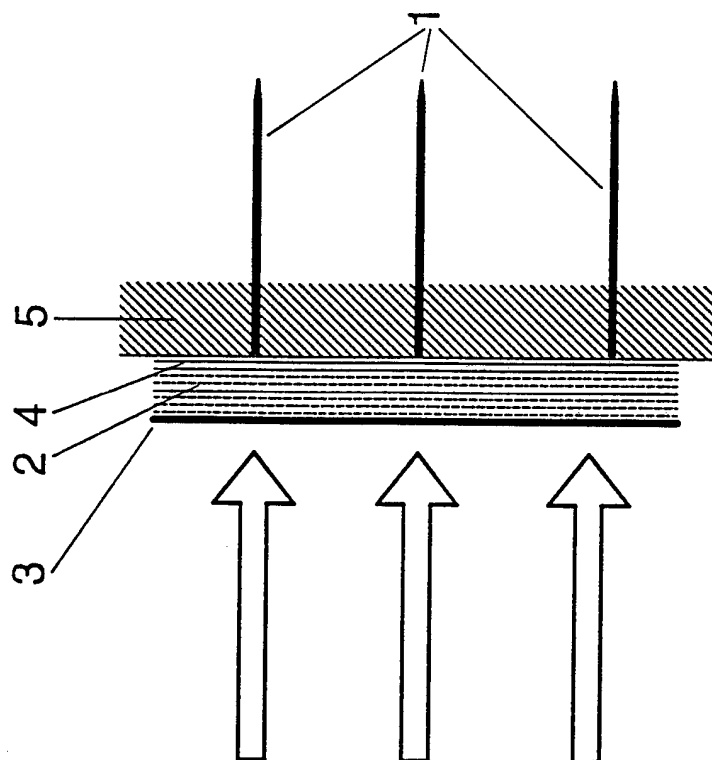


Fig. 3B

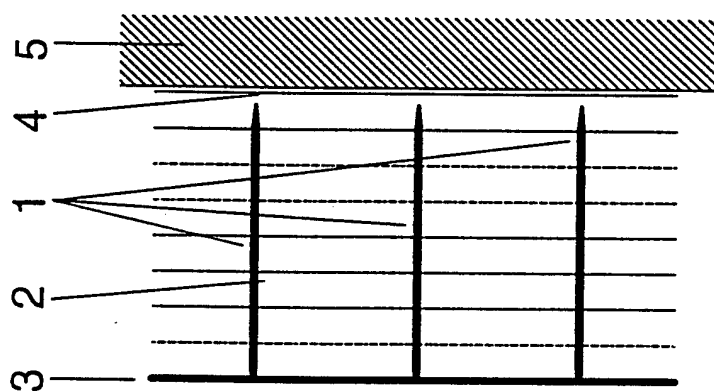


Fig. 3A



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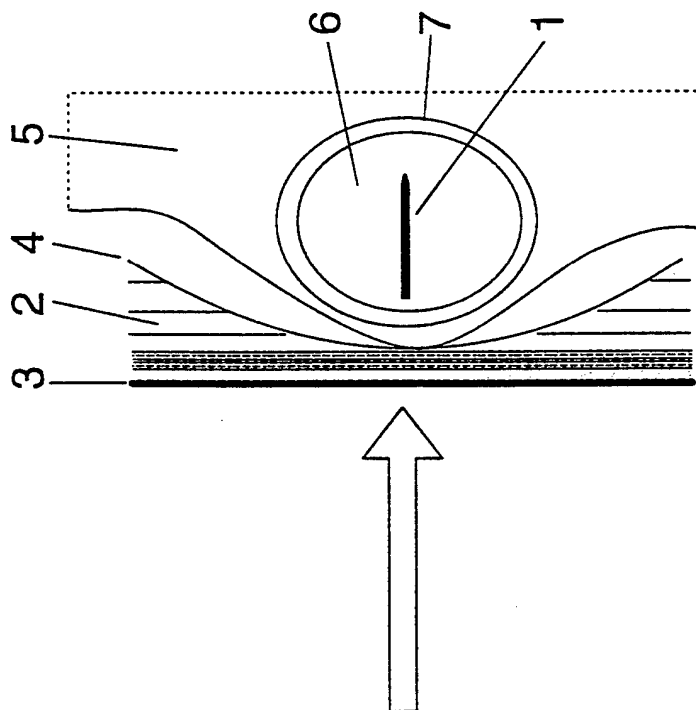


Fig. 4A

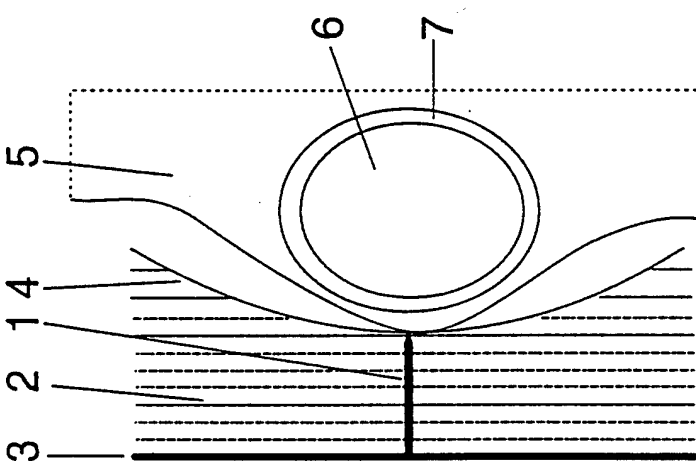


Fig. 4B

## Blood Glucose in Mini-Pigs

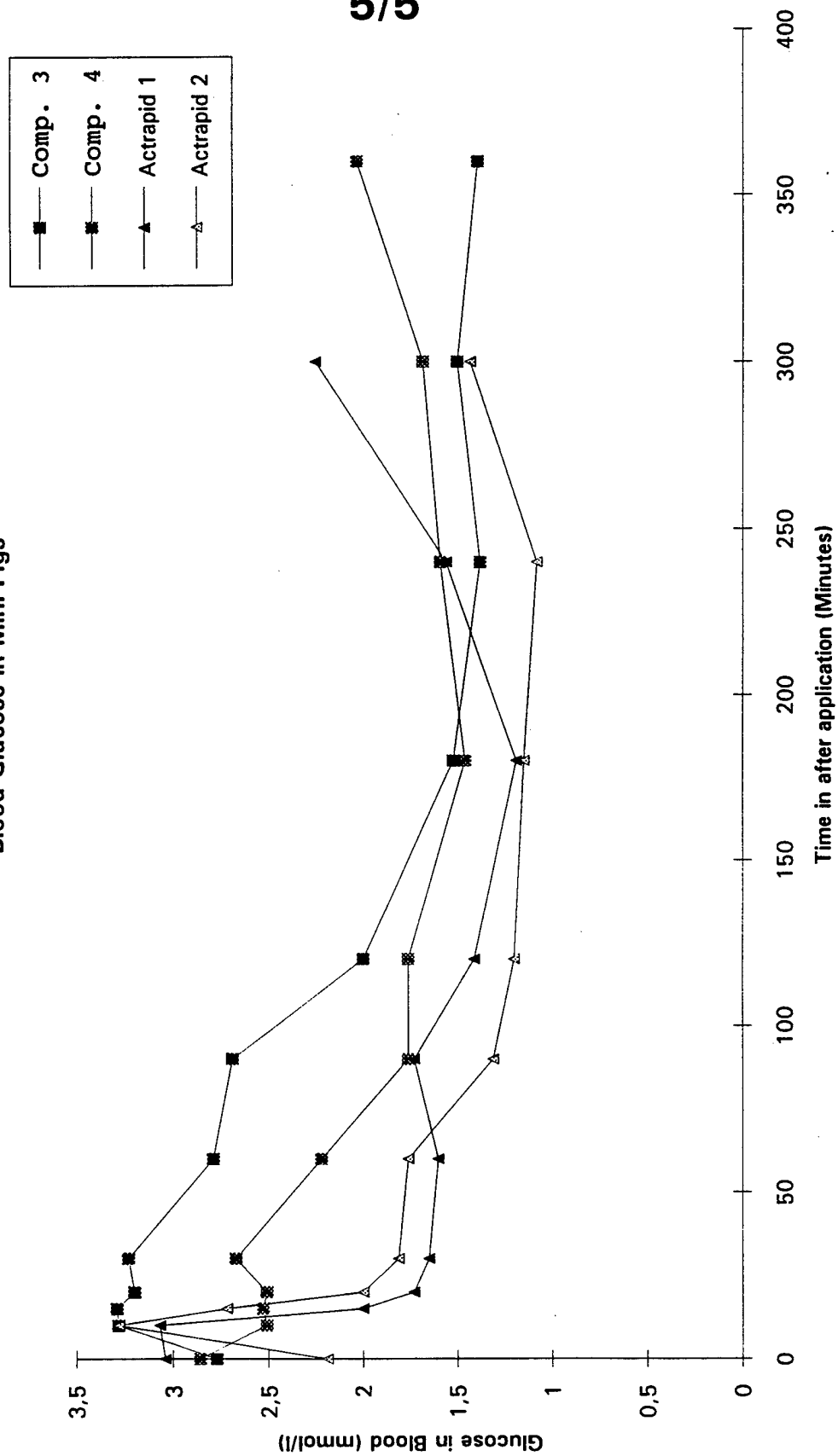


Fig. 5

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 94/00145

## A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 9/00, A61K 9/70, A61K 31/66

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K, A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, MEDLINE, WPI, WPIL, CLAIMS, CA

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CH, A5, 678272 (KABUSHIKI KAISHA ARS JAPAN), 30 August 1991 (30.08.91)  --	1-19,39-60
X	BIOMAT., ART. CELLS, ART. ORG., Volume 16, No 4, 1988, Shan-Yang Lin et al, "Controlled release of adriamycin HCl from polymeric needle devices", page 801 - page 814, see fig 1-2; page 803, line 19 - page 805, line 11  --	1-9,11-13, 16-19,39, 48-60
X	BIOMAT., ART. CELLS, ART. ORG., Volume 17, No 2, 1989, S. Y. Lin et al, "TUMORICIDAL EFFECT OF CONTROLLED-RELEASE POLYMERIC NEEDLE DEVICES CONTAINING ADRIAMYCIN HCl IN TUMOR-BEARING MICE", page 189 - page 203, see fig 1; page 190, line 8 - line 22  --	1-9,11-13, 16-19,39, 48-50,59-60

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

14 July 1994

Date of mailing of the international search report

20 -07- 1994

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Anneli Jönsson

Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 94/00145

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>Dialog Information Services, File 351, World Patent Index 81-94, Dialog accession no. 003880810, WPI accession no. 84-026348/05, MITSUI TOATSU CHEM INC: "Sustained release rod-like moulded drug mfr. by adding drugs to melt of polylactic acid or lactic-acid glycolic acid copolymer and moulding mixt". JP 58216117, A, 831215, 8405 (Basic)</p> <p>--</p>	<p>1-9,11-13, 16-19,39, 48-50,60</p>
A	<p>EP, A2, 0139286 (SUMITOMO CHEMICAL COMPANY, LIMITED), 2 May 1985 (02.05.85)</p> <p>--</p> <p>-----</p>	<p>1-19,39-60</p>

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 94/00145

**Box I** Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 20-38  
because they relate to subject matter not required to be searched by this Authority, namely:  
Methods for treatment of the human or animal body by surgery  
or therapy, as well as diagnostic methods (see PCT Rule 39.1(iv)).
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/94

International application No.

PCT/DK 94/00145

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A5- 678272	30/08/91	DE-A- 3834944	26/04/90
		US-A- 5164186	17/11/92
EP-A2- 0139286	02/05/85	SE-T3- 0139286	
		DE-A- 3484951	26/09/91
		DE-A- 3486029	18/02/93
		EP-A,B- 0138216	24/04/85
		SE-T3- 0138216	
		EP-A,B- 0140255	08/05/85
		SE-T3- 0140255	
		JP-C- 1713509	27/11/92
		JP-B- 3072046	15/11/91
		JP-A- 60097918	31/05/85
		US-A- 4774091	27/09/88
		US-A- 4855134	08/08/89
		US-A- 5021241	04/06/91
		US-A- 5081156	14/01/92
		JP-A- 60126217	05/07/85
		JP-A- 60227772	13/11/85
		JP-A- 60129057	10/07/85